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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,422	11/07/2006	Eggert Stockfleth	50125/084002	7550

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EXAMINER	
MI, QIUWEN	
ART UNIT	PAPER NUMBER
1655	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/574,422	STOCKFLETH, EGGERT	
	Examiner	Art Unit	
	QIUWEN MI	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 8-36* is/are pending in the application.

4a) Of the above claim(s) *33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6, 8-32, 35, and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's reply filed on 9/29/09 is acknowledged, with the cancellation of Claims 2 and 7. Claims 1, 3-6, and 8-36 are pending. Claims 33 and 34 are withdrawn. **Claims 1, 3-6, 8-32, 35, and 36 are examined on the merits.**

Any rejection that is not reiterated is hereby withdrawn.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 8-32, and 36 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 8, 16, 18, 23-27, and 30-33 of copending Application No. 10/682, 612. Although the conflicting claims are not identical, they are not patentably distinct from each other because actinic keratosis in case 10/682,612 is a species of the broad genus "pre-cancerous lesions" in the instant case, thus claims 1-6, 8, 16, 18, 23-27, and 30-33 of copending Application No. 10/682, 612 'anticipate' the Claims 1, 6, 8-32, and 36 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections –35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-5, and 8-20 remain rejected under 35 USC § 102 (b) as being anticipated by Yanaga et al (Yanaga et al, Prevention of carcinogenesis of mouse mammary epithelial cells RIII/MG by epigallocatechin gallate, International journal of molecular medicine 10: 311-315, 2002), as evidenced by Dou et al (US 2002/0151582)*.

This rejection is maintained for reasons of record set forth in the Office Action mailed out on 6/29/09, repeated below. Applicants' arguments filed have been fully considered but they are not deemed to be persuasive.

Yanaga et al teach "The chemopreventive effect of the polyphenols abundant in green tea on carcinogenesis has been attracting attention in recent years. Among tea polyphenols, epigallocatechin gallate (EGCG) has been studied as a preventive substance for carcinogenesis. We investigated the chemopreventive effect in a group treated with EGCG in vitro and in vivo using mouse mammary epithelial cells RIII/MG (thus skin lesion) (thus not caused by papilloma

virus, not a lesion selected from the group consisting of phyperplasia, Condyloma acuminata, warts and cervical intra-epithelial neoplasia). In the in vitro experiment, crude catechin (catechin) containing 50% or more EGCG significantly inhibited the growth of RIII/MG cells, which were precancerous cultured cells. Many cells died, and a DNA ladder was observed. In the in vivo experiment, RIII/MG cells formed a tumor after 13 weeks in a group without catechin treatment, and the tumor formation rate in the 20th week was 40%. In a group treated with 0.1% catechin, a tumor began to grow in the 13^{th} week, and the tumor formation rate in the 20th week was 20%. In a group treated with 1% catechin, no tumor was detected even in the 20th week. Yanaga et al teach in mice not given catechin, a tumor formed in 25-30% of animals in the 18-20 th week after transplanation of precancerous RIII/MG cells. The tumors that formed were histopatholigically cancerous, suggesting that the precancerous cells grew subcutaneously in nude mice and developed into cancer cells during the formation of the phyma. In contrast, tumor formation was inhibited in mice treated with catechin in a concentration dependent manner. No tumor was formed in the group treated with a high concentration of catechin. There was no significant difference in the change in body weight between the catechin treatment groups and the non-treatment group during the observation period. Tissue samples were stained by the nick-end-labeling method and apoptosis was observed in many cells. Based on the above findings, EGCG inhibited growth in the mouse viral mammary epithelial carcinogenesis model RIII/MG, and induced apoptosis, suggesting a clinical usefulness of EGCG as a chemopreventive substance" (see Abstract). Yanaga et al also teach "this study showed that EGCG inhibited the growth and induced apoptosis in precancerous mammary RIII/MG cells in vivo, as observed in vitro" (page 314, 1st column, last paragraph).

As evidenced by Dou et al, green tea contains polyphenol compounds EGCG (formula I and II in claims 13 and 14 are thus met), ECG, GCG, or CG (claim 3).

Therefore, the reference is deemed to anticipate the instant claim above.

Claim Rejections –35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-5, and 8-26 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yanaga et al (Yanaga et al, Prevention of carcinogenesis of mouse mammary epithelial cells RIII/MG by epigallocatechin gallate, International journal of molecular medicine 10: 311-315, 2002), as evidenced by Dou et al (US 2002/0151582)*.

This rejection is maintained for reasons of record set forth in the Office Action mailed out on 6/29/09, repeated below. Applicants' arguments filed have been fully considered but they are not deemed to be persuasive.

Yanaga et al teach "The chemopreventive effect of the polyphenols abundant in green tea on carcinogenesis has been attracting attention in recent years. Among tea polyphenols, epigallocatechin gallate (EGCG) has been studied as a preventive substance for carcinogenesis. We investigated the chemopreventive effect in a group treated with EGCG in vitro and in vivo

using mouse mammary epithelial cells RIII/MG (thus skin lesion) (thus not caused by papilloma virus, not a lesion selected from the group consisting of phyperplasia, Condyloma acuminata, warts and cervical intra-epithelial neoplasia). In the in vitro experiment, crude catechin (catechin) containing 50% or more EGCG significantly inhibited the growth of RIII/MG cells, which were precancerous cultured cells. Many cells died, and a DNA ladder was observed. In the in vivo experiment, RIII/MG cells formed a tumor after 13 weeks in a group without catechin treatment, and the tumor formation rate in the 20th week was 40%. In a group treated with 0.1% catechin, a tumor began to grow in the 13^{th} week, and the tumor formation rate in the 20th week was 20%. In a group treated with 1% catechin, no tumor was detected even in the 20th week. Yanaga et al teach in mice not given catechin, a tumor formed in 25-30% of animals in the 18-20 th week after transplanation of precancerous RIII/MG cells. The tumors that formed were histopatholigically cancerous, suggesting that the precancerous cells grew subcutaneously in nude mice and developed into cancer cells during the formation of the phyma. In contrast, tumor formation was inhibited in mice treated with catechin in a concentration dependent manner. No tumor was formed in the group treated with a high concentration of catechin. There was no significant difference in the change in body weight between the catechin treatment groups and the non-treatment group during the observation period. Tissue samples were stained by the nick-end-labeling method and apoptosis was observed in many cells. Based on the above findings, EGCG inhibited growth in the mouse viral mammary epithelial carcinogenesis model RIII/MG, and induced apoptosis, suggesting a clinical usefulness of EGCG as a chemopreventive substance" (see Abstract). Yanaga et al also teach "this study showed that EGCG inhibited the

growth and induced apoptosis in precancerous mammary RIII/MG cells in vivo, as observed in vitro" (page 314, 1st column, last paragraph).

As evidenced by Dou et al (US 2002/0151582), green tea contains polyphenol compounds EGCG (formula I and II in claims 13 and 14 are thus met), ECG, GCG, or CG (claim 3).

Yanaga et al do not teach the claimed amounts of the polyphenols in the composition.

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use the inventions of Yanaga et al since they provide scientific data for green tea extract on chemoprevention of precancerous cells, one of ordinary skill in the art would have been motivated to make the modifications. The result-effective adjustment in conventional working parameters (e.g., determining an appropriate amount of the each polyphenol components as claimed isolated from green tea within the composition) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. The differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference

process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). see MPEP § 2144.05 part II A. Although the prior art did not specifically disclose the amounts of each catechin constituent, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal concentrations of components because concentrations of the claimed components are art-recognized result effective variables because they have the ability to prevent of carcinogenesis of mouse mammary precancerous cells, which would have been routinely determined and optimized in the pharmaceutical art.

Since the mouse mammary epithelial cells RIII/MG is not caused by papilloma virus, not a lesion selected from the group consisting of phyperplasia, Condyloma acuminata, warts and cervical intra-epithelial neoplasia, thus the limitation of claims 4-5 is met.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Claims 1, 4-6, 8-32, and 35 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yanaga et al and Dou et al as applied to claims 1, 4-5, and 8-26 above, and further in view of Brash et al (US 2002/0198161), and further in view of Voet (US 6,723,750).

This rejection is maintained for reasons of record set forth in the Office Action mailed out on 6/29/09, repeated below. Applicants' arguments filed have been fully considered but they are not deemed to be persuasive.

The teachings of Yanaga et al and Dou et al are set forth above and applied as before.

The combination of Yanaga et al and Dou et al do not specifically teach topical application of green tea extract, additive isopropyl myristate, form of ointment, or combined with different treatment curettage, or the claimed amount of the polyphenols.

Brash et al teaches that skin precancers are being treated, the preferred mode of administration is topical. The topical application may contain carrier, excipient or vehicle ingredients such as isopropyl myristate etc., and mixtures thereof to form lotions, creams, emulsions, gels, or ointments [0086]. Brash et al also teaches a method of preventing a precancer, cancer, hyperproliferative or benign dysproliferative disorder in a human subject (claim 76).

Voet teaches that the current management options for visible or easily perceived and diagnosed precancerous dermatological lesions such as Aks (thus claim 35 is met) include cryosurgery with liquid nitrogen, topical treatment, and curettage (col 2, lines 15-20). Voet also teaches that curettage, which involves the use of a curette to scrape away the lesion, is another common method of treatment for easily perceptible precancerous skin lesions. The primary advantage of curettage is the ability to submit the specimen for histologic analysis.

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use the carrier isopropyl myristate and ointment form for human subject from Brash et al, and the treatment of curettage from Voet in the current invention since carrier isopropyl myristate and ointment form are the conventional carrier and pharmaceutical form that have been used successfully in treating precancerous lesions in the topical route according to Brash et al; and combining the treatment curettage from Voet with the topical could monitor the histologic status of the tissue treated by topical administration. Since both Brash et al, and the treatment of curettage from Voet yielded beneficial results in treating precancerous lesions, one of ordinary skill in the art would have been motivated to make the modifications to combine the references together.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Claims 1, 4-6, 8-20, and 36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yanaga et al and Dou et al as applied to claims 1, 4-5, and 8-20 above, and further in view of An Kathy et al (Cyclooxygenase-2 expression in murine and human nonmelanoma skin cancers: implications for therapeutic approaches, Photochemistry and photobiology, (2002 Jul) Vol. 76, No. 1, pp. 73-80).

This rejection is maintained for reasons of record set forth in the Office Action mailed out on 6/29/09, repeated below. Applicants' arguments filed have been fully considered but they are not deemed to be persuasive.

The teachings of Yanaga et al and Dou et al are set forth above and applied as before.

The combination of Yanaga et al and Dou et al do not specifically teach treating actinic keratosis.

An Kathy et al teach COX-2 expression was also increased in human actinic keratoses. An Kathy et al also teach acute exposure of the human skin to UVB (minimum erythema dose x 4) caused a transient enhancement of the COX-2 expression, which reverted to baseline within hours; however, in murine skin the expression persisted for several days. Pretreatment with the topically applied green tea extract (1 mg/cm2) largely abrogated the acute COX-2 response to UVB in mice or humans. In summary, enhanced COX-2 expression serves as a marker of epidermal UVB exposure for murine and human NMSC. These results suggest that COX-2 inhibitors could have potent anticarcinogenic effects in UVB-induced skin cancer (see Abstract).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use the green tea extract to treat actinic keratoses from An Kathy et al since An Kathy et al teach green tea extract (1 mg/cm2) largely abrogated the acute COX-2

response to UVB in mice or humans. Since both Yanaga et al and An Kathy et al teach using green tea extract to treat precancerous lesion, one of ordinary skill in the art would have been motivated to make the modifications and combine the two references together.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

*This reference is cited merely to relay an intrinsic property and is not used in the basis for rejection *per se.*

Claims 1, 3-6, 8-32, and 35 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Yanaga et al, Dou et al, Brash et al, and Voet as applied to claims 1, 4-6, 8-32, and 35 above, and further in view of Araki et al (Araki et al, Chemoprevention of mammary preneoplasia, In vitro effects of a green tea polyphenol, Annals of the New York Academy of Sciences 768: 215-222, 1995).

The teachings of Yanaga et al, Dou et al, Brash et al, and Voet are set forth above and applied as before.

The combination of Yanaga et al, Dou et al, Brash et al, and Voet do not specifically teach treating a non-virally induced precancerous lesion of the skin using a polyphenol.

Araki et al examine the extent of preneoplastic and neoplastic transformation in mouse mammary epithelial cells initiated for tumorigenic transformation by deregulated expression of c-myc oncogene or of MTV (mammary tumor virus) (page 215, last paragraph). Araki et al teach

a continuous 14 day treatment of MMEc/myc3 cells with 1.0 μg/ml EGCG resulted in a 25% inhibition ($p< 0.0001$) in the number of anchorage-independent colonies. Treatment of RIII/MG cells with 0.1 μg/ml EGCG resulted in an 88.9% inhibition ($p = 0.0001$) in the number of anchorage-independent colonies (page 217, last paragraph). Araki et al teach AIG represents a useful in vitro biomarker forpreneoplastic and neoplastic transformation. The data generated from the present study essentially confirm and extend our previous observations and indicate that nontumorigenic mammry epithelial cells, upon initiation by c-myc oncogene or MTV, express AIG in vitro and tumorigenesis in vivo. Furthermore, because AIG is detected in initiated MMEC/myc3 and RIII/MG cells as well as in tumor-derived MMEC/myc3-Pr1 and RIII/Pr1 cells, upregulation of AIG in cells initiated by c-myc oncogene or by MTV represents a marker for preneoplastic transformation (page 218, last paragraph bridging page 219). Araki et al teach the aqueous extract of green tea provides a complex mixture of polyphenols, caffeine, and thrombin. Among the polyphenols, EGCG represents a major water-soluble fraction of the tea extract. The aqueous extract of tea as well as the major polyphenolic component, EGCG, suppress procarcinogen-induced organ-site tumorigenesis in vivo. During the multistage development of organ-site cancer, EGCG is reported to influence carcinogen activation and DNA adduct formation, as well as generation of free-radical mediated oxidative DNA damage, all of which are critical targets for initiation of carcinogenesis. In addition, EGCG is reported to affect the promotional stage of carcinogenesis in part via molulation of p450-dependent enzymes critical for sustained proliferative activity of the initiated phenotype. This aspect of the biological activity of EGCG appears to be more relevant of the present study because AIG represents a late-occurring, postinitiation event in the multistage process of carcinogenesis. The experiments

designed to examine the effect of EGCG on initiated MMEC/myc3 and RIII/MG cells revealed a dose-dependent suppression of proliferation in the anchorage-dependent condition of growth. It was also noteworthy that the optimal antiproliferative dose of EGCG differed by at least 10-fold in the two cell lines. The oncogene-initiated cells required a 10-fold higher dose of EGCG than the virus-initiated cells to suppress AIG. This differential responsiveness may be attributed to the type of initiator. In this context, it is notable that deregulated expression of c-myc oncogene in transgenic mice results in early onset of mammary adenocarcinomas, whereas MTV is considered a weakly transforming retrovirus that produces slow-growing mammary adenocarcinomas in vivo. These observations, together with our data on the differential responsiveness of MMEC/myc3 and RIII/MG cells to EGCG, raise the possibility that the potency of the oncogene being higher concentration of EGCG for its preventive efficacy. Clearly, this aspect needs to be systematically analyzed by mechanism-oriented experiments (page 219, last paragraph bridging page 220).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use EGCG to treat oncogene-intiated RIII/MG cells since Araki et al teach EGCG is effective in both oncogene or virus initiated MMEC/myc3 and RIII/MG cells. Since all the references teach using green tea extract to treat precancerous lesion, one of ordinary skill in the art would have been motivated to make the modifications and combine the references together.

From the teachings of the references, it is apparent that one of the ordinary skills in the art would have had a reasonable expectation of success in producing the claimed invention.

Thus, the invention as a whole is *prima facie* obvious over the references, especially in the absence of evidence to the contrary.

Applicant argues that "The present claims are directed to a method of treating precancerous lesions of the skin of a patient (e.g., actinic keratoses) by administration of a polyphenol-containing composition to a patient. In contrast to the pending claims, Yanaga teaches the prevention of viral carcinogenesis in mouse mammary epithelial cells that are initiated with mouse mammary tumor virus (MMTV). This distinction is first highlighted by the title of Yanaga, "Prevention of Carcinogenesis of Mouse Mammary Epithelial Cells RIII/MG by Epigallocatechin Gallate" (emphasis added). Moreover, throughout Yanaga, prevention or protection against subsequent viral carcinogenesis is repeatedly discussed. For example, Yanaga describes the "[p]revention of cancer development by EGCG in RIII/MG-transplanted nude mice" (page 312 of Yanaga, left column) and the inhibition of tumor growth by catechins *in vitro and in vivo* (pages 312-313 of Yanaga). Indeed, Yanaga concludes that "green tea ingested in daily life may be a preventive drug against breast cancer" (page 314 of Yanaga, right column; emphasis added)" (page 2, last paragraph bridging page 3).

First of all, RIII/MG cells are initiated with mouse mammary tumor virus, thus claim 3 is withdrawn from the previous rejections. However, Mammary epithelial cells are mammary skin cells, thus they fall into the category of skin cells. Further more, the "Prevention of

Carcinogenesis of Mouse Mammary Epithelial Cells RIII/MG by Epigallocatechin Gallate" is through the treatment of pre-cancerous lesion, which is consistent with the current claims.

Applicant argues that "Further, with respect to claim 3, Yanaga teaches that RIII/MG cells are generated by infection with mouse mammary tumor virus. In contrast to Yanaga, the precancerous skin lesions (e.g., actinic keratoses) of the present claims are not virally induced. For the record, Applicant notes that catechols (in particular, EGCG) are known to have antiviral properties, most likely due to their inhibitory effect on reverse transcriptase (see, e.g., Yamaguchi et al., *Antiviral Research* 53: 19-34, 2002; herein "Yamaguchi" and submitted with this Reply). Thus, the observed chemopreventive effect of catechins on the RIII/MG and RIII/Pr-1 cells of Yanaga may be the result of the antiviral activity associated with such compounds' (page 3, 2nd paragraph).

This is found persuasive. Therefore, the rejections over claim 3 have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Araki et al.

Applicant argues that "Finally, Applicant notes that the present claims are directed to treating precancerous lesions of the skin of a patient. The RIII mouse mammary epithelial cells used in the experiments of Yanaga are not skin cells, and viral carcinogenesis of RIII mouse mammary epithelial cells would not result in the development of a precancerous skin lesion. For this reason as well, Yanaga fails to anticipate the claims of the present invention" (page 3, 3rd paragraph).

This is not found persuasive. Mammary epithelial cells are mammary skin cells, thus they fall into the category of skin cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Qiuwen Mi whose telephone number is 571-272-5984. The examiner can normally be reached on 8 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Qiuwen Mi/

Examiner, Art Unit 1655